REMARKS

Claims 17-18 and 36-42 are amended. Claims 1-16, 19, 21, 27-35 are cancelled. Claim 33 has been amended and renumbered as claim 45. Claims 17-18, 20, 22-26, and 36-45 are pending. Support for the amendments to the claims may be found in the specification and the originally presented claims. Inventorship of the pending claims has not changed.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Priority

The Office Action stated that priority to USSN 60/345,805, filed January 4, 2002, could not be claimed by USSN 10/338,083, filed on January 6, 2003. The Office Action stated that USSN 60/345,805 expired on January 4, 2003. Applicants respectfully disagree.

35 U.S.C. § 119(e)(3) states: "If the day that is 12 months after the filing date of a provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, the period of pendency of the provisional application shall be extended to the next succeeding secular or business day." January 4, 2003 was a Saturday, and thus the pendency of USSN 60/345,805 was extended until Monday, January 6, 2003. Applicants respectfully submit that denial of the benefit of the January 4, 2002 filing date is improper and request reconsideration of the claim of priority to USSN 60/345,805.

Specification

The disclosure was objected to for informalities. Claims 39-42 have been amended to recite "SEQ ID NO: 1" for TNFA. The disclosure has been amended to include "SEQ ID NO:" references for members of the TNF Super Family. Applicants respectfully request withdrawal of the objection.

Double Patenting

Claims 17, 18, 20, 23-26, 36-45 are provisionally rejected under the nonstatutory doctrine of obviousness-type double patenting as unpatentable over claims 50-58 and 64-72 of copending Application No. 09/981,289, claims 1-16 of copending Application No. 10/963,994, and claim 1 of copending Application No. 11/008,091. As copending applications, the instant application and Application Nos. 09/981,289, 10/963,994, and 11/008,091 are subject to further

amendments. Such amendments may render the grounds for the present rejection moot and obviate any terminal disclaimers.

Applicants respectfully request that the instant rejection be held in abeyance until allowable subject matter has been found in the instant application or Application Nos. 09/981,289, 10/963,994, and 11/008,091 have issued as patents.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 17-26 and 36-45 are rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 19 and 21 are cancelled, rendering rejection of these claims moot. Applicants respectfully submit that the specification does in fact reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed.

Claim 17 has been amended to point out specifically that a variant TNFSF protein comprises "at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain." Claim 17 also recites "[a] mixed TNFSF oligomer [that] has at least a 50% decrease in receptor activation as compared to a homotrimer of [a] naturally occurring TNFSF protein." Claim 18 recites "a mixed TNFSF oligomer [that] has at least a 90% decrease in receptor activation as compared to [a] naturally occurring TNFSF oligomer." Applicants submit that the instant application provides specific guidance as to the changes that should be made to produce TNFSF variants.

The specification fully supports the claimed amino acid substitutions in the Large Domain, the Small Domain and the DE Loop. "The Large Domain, the Small Domain and the DE loop are three separate receptor contact domains, each made up of several non-contiguous linear segments of the protein[.]" Specification, p. 14, lines 37-39. On page 15, lines 11-12, the specification states that "[t]he Large Domain preferred positions to be modified in TNFSF proteins include but are not limited to TNFA corresponding positions 28-34, 63-69, 112-115, and 137-147. For the Small Domain, the preferred positions to be modified include but are not limited to TNFA corresponding positions 72-79 and 95-98. For the DE Loop, the preferred positions to be modified include but are not limited to TNFA corresponding positions 84-89."

Furthermore, substitutions at multiple positions in combinations of these domains are disclosed. For example, the specification on page 16, lines 20-22, states that examples of substitutions in multiple domains include "simultaneous substitution of amino acids at the large

and small domains (e.g. MSA positions 94 and 112), [and] large domain and DE loop (e.g. MSA positions 95 and 124)[.]"

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. MPEP § 2163 II.A.3.a.ii. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. MPEP § 2163 II.A.3.a.ii.

The specification clearly demonstrates that Applicants were in physical possession of non-naturally occurring TNFSF variants that meet the limitations of independent claims 17 and 18, as amended, for several TNFSF members, such as TNF-α in Example 7 and RANKL. In example 7, three different TNF-alpha variants – A145R, A145R/Y87H, and triple variant E146K/V91E/N34E – were tested. Results in Figure 4A show that all three variants were effective in decreasing TNF-alpha induced NFkB activation, meaning that each TNF-alpha variant had effectively exchanged with wild type TNF-alpha. Further experiments show that A145R/Y87H TNF-alpha variant that has formed a heterotrimer with wild type TNF-alpha results in the inability of the TNF-alpha oligomer to induce NFkB nuclear translocation. Specification, p. 51, lines 32-37.

Variants of RANKL, another protein in the TNFSF class, were experimentally found to form heterotrimers with wild type RANKL. Dominant-negative RANKL variants were designed by substituting amino acids at key RANKL-RANK contact points with amino acids that disrupt the ability of the ligand to activate receptor. Specification, p. 52, lines 34-35. RANKL variants were then expressed, purified and screened using the TRAP assay, which monitors osteoclastogenesis in RAW264.7 cells. Specification, p. 53, lines 34-36. Osteoclastogenesis is antagonized by heterotrimeric variant:wild-type RANKL. The TRAP assay identified the nine antagonizing variants shown in Figure 7G.

The specification further discusses variants of numerous members of the TNF Super Family. Specifically, BLyS, CD40L, APRIL and OX-40 are disclosed on page 55, lines 19-24, where the protocol described for selecting RANKL variants equally applies to these TNFSF variants, which exchange with their corresponding wild type TNFSF member. Figure 3 shows in detail the sequence alignment for 17 different members of TNFSF, including BLyS, CD40L, APRIL and OX-40. Figure 3 also highlights 7 canonical receptor contact regions based on analysis of known structures and mutational data. The Large Domain, Small Domain and the DE loop are three separate receptor contact domains, each made up of several non-contiguous

linear segments of the protein (i.e. the 7 canonical receptor contact regions). Specification, p. 14, lines 37-39. The specification on page 14, lines 23-25, states that each of the 7 regions highlighted in Figure 3 as a receptor-contact region is used to define modification sites for the creation of variants of each TNFSF member. Furthermore, TNFA corresponding positions 57, 34 and 91 are identified as preferred trimer interface positions for modification. Specification, p. 15, lines 17-18. The sequence alignment in Figure 3 allows for ready identification of TNFA corresponding positions in any of the 17 different members of TNFSF, which positions can then be used for modification. See Specification, p. 15, lines 24-28.

Applicants respectfully submit that one of skill in the art, upon reading the specification, would conclude that as of the filing date of the patent application, Applicants were in possession of the claimed invention. Applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claim 33 (presently claim 45) is rejected as being indefinite. Claim 45 has been amended to refer to claims 18-26 in the alternative. Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejection of original claim 33, as amended and renumbered as claim 45.

Claim Rejections – 35 U.S.C. § 101

Claims 17-26 and 36-45 are rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Specifically, the Office Action asserts that the claim, as written, encompass molecules that may already be present in nature. Claims 19 and 21 are canceled, rendering rejection of these claims moot. Independent claims 17-18 have been amended to clarify that the variant TNFSF proteins are "non-naturally occurring". Remaining claims 20, 22-26 and 36-45 depend from amended claim 18.

Applicants respectfully request the rejection of claims 17-18, 20, 22-26, and 36-45 under 35 U.S.C. § 101 be withdrawn.

Claim Rejections – 35 U.S.C. § 102

Claims 17, 18, 20, 22-26, 36-45 are rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent 6,171,787 (the '787 patent) to Wiley and 5,716,805 (the '805 patent) to Srinivasan et al. Claims 19 and 21 are cancelled, rendering rejection of these claims moot.

The '787 patent does not anticipate the present claims as amended. Claim 18 has been amended to claim a "non-naturally occurring variant TNFSF protein comprising at a variant extracellular domain of a TNFSF protein, wherein said variant TNFSF protein will interact *in vivo* with a naturally occurring TNFSF oligomer to form a mixed TNFSF oligomer, and wherein said mixed TNFSF oligomer has at least a 90% decrease in receptor activation as compared to said naturally occurring TNFSF oligomer." The '787 patent discloses a naturally occurring TNFSF protein with non-conservative mismatches. Furthermore, nowhere does the '787 patent disclose that a non-naturally occurring TNFSF having at least a 90% decrease in receptor activation as compared to a naturally occurring TNFSF oligomer.

Claim 17 has been amended to claim a "mixed TNFSF oligomer comprising at least one non-naturally occurring variant TNFSF protein comprising at least a variant extracellular domain of a TNFSF monomer protein and a naturally occurring TNFSF protein, wherein said variant TNFSF protein comprises an amino acid sequence that has at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain, and wherein said mixed TNFSF oligomer has at least a 50% decrease in receptor activation as compared to a homotrimer of said naturally occurring TNFSF protein." The '787 patent only discloses purified, naturally occurring TNFSF proteins, whereas claim 17 claims a mixed TNFSF oligomer comprising at least one non-naturally occurring variant TNFSF protein. The '787 patent further does not disclose a mixed TNFSF oligomer having at least a 50% decrease in receptor activation as compared to a homotrimer of a naturally occurring TNFSF protein. The '787 patent also does not teach making at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain.

Since the '787 patent does not teach or disclose a molecule that possesses all the limitations of claims 17 and 18, as amended, and claims 20, 22-26, 36-45 depending from them, the '787 patent cannot anticipate the pending claims.

The '805 patent does not teach or suggest all the limitations of claims 17 and 18, as currently amended, and thus cannot anticipate the pending claims. The '805 patent describes constructs of fusion proteins. The '805 patent does not disclose a variant TNFSF protein comprising an amino acid sequence that has at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain. The '805 patent also does not disclose any mixed

TNFSF oligomer having at least a 50% or 90% decrease in receptor activation compared to a homotrimer of a naturally occurring TNFSF protein.

The '805 patent does not teach or suggest all the limitations of claims 17 and 18, as currently amended, nor of claims 20, 22-26, 36-45 depending from them, and thus cannot anticipate the pending claims.

Applicants respectfully request the rejection under 35 U.S.C. § 102 be withdrawn.

The Examiner is invited to contact the undersigned at (626) 737-8089 if any issues may be resolved in that manner.

Respectfully submitted,
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